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A comparison of two treatment regimes for the treatment of fungal eye infections in East Africa

Submission date	**Recruitment status**	[X] Prospectively registered
19/08/2020	No longer recruiting	[X] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
27/08/2020	Completed	[_] Results
Last Edited	**Condition category**	[_] Individual participant data
11/06/2025	Eye Diseases	[X] Record updated in last year

Plain English summary of protocol

Background and study aims

Infection of the clear part of the front of the eye (the cornea) is a corneal ulcer. It is an important cause of blindness in East Africa. A scratch in the cornea allows infection to enter and an ulcer to begin. These infections can be very serious with some people losing the sight in the affected eye. Different types of infectious organisms can cause corneal ulcers. These include bacteria and fungi. In tropical regions about half of all corneal ulcers are caused by fungi. Bacteria and fungi need to be treated with different types of eye drop medicines.

Treatments for fungal eye infections are frequently not very effective, in addition access to these treatments in many countries is very limited and can be expensive. In some countries they are simply not available. Currently the most commonly used treatment for fungal corneal ulcers is an eye drop called Natamycin. There is a need for additional, alternative, affordable and more easily available eye drop treatments for fungal infections.

There is an antiseptic solution called Chlorhexidine. This is very effective at killing bacteria, fungi and other types of infectious organisms. It is used in medical care worldwide in several different ways. For example, it is used to clean skin before surgical operations, in antiseptic creams for skin cuts and as a mouth wash to prevent and treat mouth infections. It has been used in eye care for more than thirty years as an eye-drop preservative, for sterilizing contact lenses, for pre-operative topical antiseptic and for treating Acanthamoeba and fungal corneal infections.

About twenty years ago chlorhexidine eye drops were tested in two small clinical trials conducted in India and Bangladesh for the treatment of fungal corneal infections. The results of these studies suggested that chlorhexidine was as good as and possibly better than natamycin at controlling the infection. Neither eye drop had any serious side effect. However, the studies were not large enough to be certain.

Chlorhexidine is currently used in several countries for the treatment of fungal corneal infections when natamycin or alternative treatment is not working or is not available. We are interested in whether combining natamycin with chlorhexidine will help improve the outcome in patients with fungal corneal ulcers.

We are conducting a large clinical trial to find out whether chlorhexidine 0.2% eye drops in combination with natamycin 5% are as effective as or more effective than natamycin 5% eye drops alone for treating fungal corneal infections.

Who can participate?
Adults (individuals 18 years or older) with acute fungal corneal infections confirmed on microscopy can participate, provided they meet the eligibility criteria and can give informed consent.

What does the study involve?
Consented eligible participants will initially undergo a detailed clinical assessment by an experienced ophthalmic clinician. This will include background demographic data, history, examination, investigations (corneal samples, in vivo confocal microscopy, blood tests for diabetes and HIV) and Quality of Life assessments. Participants will then be given one of two treatment regimes: chlorhexidine 0.2% and natamycin 5% eye drops, or natamycin 5% eye drops alone. These will be decided at random by a pre-prepared randomisation sequence. The clinicians involved in the care of the patient will not know which treatment the participants have been allocated to (i.e. they are "masked"). Participants will then be assessed again at a number of time points to see how they are responding to the treatment, with further investigations and clinical examinations performed as detailed in the study protocol. The final review will take place at three months. The primary outcome measure will be best spectacle corrected visual acuity at three months.

What are the possible benefits and risks of participating?
Benefits:
• The study will involve tests for the type of infection. This helps the clinician looking after the patient choose the best type of treatment by accurately diagnosing the causative organism.
• The costs for clinical assessment, tests, treatment and transport will be paid for by the study.
• By participating in this study, participants will be helping to answer the question about whether or not chlorhexidine is a suitable additional treatment for fungal corneal infections.
Risks:
1. Random Allocation and Treatment Failure: Participants will be randomly allocated to a treatment. The treatment they are allocated to may prove to be less effective or have more side effects than the other study treatment or other available treatments. It is important to recognise that corneal infection is a serious, sight threatening condition. Many patients, whatever the treatment used, have reduced vision in the affected eye after it has resolved. In some people the affected eye will become blind. Sometimes the infection, despite lots of treatment, can progress to cause a hole to develop in the cornea (perforation) and sometimes it is so severe it is necessary to perform an operation to remove the eye content.
2. Local Irritation: As with most eye drops, there is the risk of local irritation or stinging from either chlorhexidine or natamycin. This usually only lasts for a short time.
3. Allergic Response: Very rarely, either chlorhexidine or natamycin eye drops can provoke a local allergic reaction on the surface of the eye or the eyelids.
4. Pregnancy and Breast-Feeding: The risks to an unborn or breast-fed baby from antifungal eye drops use are unknown. Therefore, pregnant and breastfeeding women are excluded from participating in this study.
5. Natamycin 5% eye drops: Natamycin is an approved antifungal medication that is currently being used for the treatment of fungal corneal ulcer. It is on the World Health Organisation Essential Medicines List for the treatment of fungal corneal infections. There are no known serious side effects with this medication. It may cause mild irritation and very rarely a local allergic response.
6. Chlorhexidine 0.2% eye drops: Chlorhexidine eye drops are used on the surface of the eye as an antiseptic before procedures and also in the treatment of fungal and other eye infections. It has not been associated we any serious side effects. It may cause mild irritation and very rarely a local allergic response. This concentration of chlorhexidine is approved to be used in much larger volumes as a mouth wash. It is considered to be safe and is not associated with any systemic side

effects.
7. Procedures: including examinations, confocal microscopy, corneal sample collection and checking for the best glasses or contact lenses carry the same very small risk whether they are performed as part of this study or of usual care outside the study. To minimise discomfort, topical anaesthetic will be given before examinations and sample collection.
8. Unknown Risks: The treatments in this study may have rare side effects that are currently not known. If during the course of the study new information becomes available, the researchers will share this with.

Where is the study run from?
Kilimanjaro Christian Medical Centre, Moshi, Tanzania Mbarara Regional Referral Hospital, Mbarara, Uganda

When is the study starting and how long is it expected to run for?
April 2018 to December 2022

Who is funding the study?
Wellcome Trust, UK

Who is the main contact?
Dr Jeremy Hoffman, jeremy.hoffman@lshtm.ac.uk

Contact information

Type(s)
Public

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Type(s)
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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
LSHTM14908, WT 207472/Z/17/Z

Study information

Scientific Title
Randomised controlled trial of topical combination therapy chlorhexidine 0.2% and natamycin 5% versus topical natamycin 5% alone for fungal keratitis in East Africa

Study objectives
Current study hypothesis as of 08/09/2021:

Treatment with combined g. chlorhexidine 0.2% and g. natamycin 5% is superior to g. natamycin 5% alone for the treatment of fungal keratitis in terms of best spectacle corrected visual acuity at 3 months

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Previous study hypothesis:

G-chlorhexidine 0.2% is non-inferior to g-natamycin 5% for the treatment of fungal keratitis

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Approved 04/04/2018, London School of Hygiene and Tropical Medicine Ethics Committee (London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT; +44 (0) 2076368636; ethics@lshtm.ac.uk), ref: 14908
2. Approved 14/08/2019, Kilimanjaro Christian Medical College Research Ethical Clearance (Kilimanjaro Christian Medical College, PO Box 2240, Moshi, Tanzania; no telephone number provided; no email provided), ref: 2431
3. Approved 14/05/2019, National Institute for Medical Research (National Institute for Medical Research, 3 Barack Obama Drive, PO Box 9653, 11101 Dar Es Salaam, Tanzania; +255 22 2121400; nimrethics@gmail.com), ref: NIMR/HQ/R.8A/Vol. IX/3091

4. Approved 05/09/2019, Mbarara University of Science and Technology Research Ethics Committee (Mbarara University of Science and Technology, PO Box 1410, Mbarara, Uganda; +256 4854 33795; sec.rec@must.ac.ug), ref: MUREC 1/7
5. Approved 05/08/2019, Uganda National Council for Science and Technology (Uganda National Council for Science and Technology, Plot 6, Kimera Road, Ntinda, PO Box 6884, Kampala, Uganda; +256 414 705500; info@uncst.go.ug), ref: HS 2514

Study design
Randomized controlled single-masked two-armed trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
See additional files

Health condition(s) or problem(s) studied
Fungal keratitis

Interventions
Current interventions as of 08/09/2021:

Participants will be randomised to either combined topical chlorhexidine 0.2% and topical natamycin 5% or topical natamycin 5% alone. The treatment will be given hourly for one week, then two-hourly for a further two weeks. Ongoing treatment duration will then be tailored by clinical response. Follow-up assessments will be conducted at 2 days, 1 week, 2 weeks, 3 weeks, 2 months and 3 months, to determine the outcome. Randomisation, Allocation Concealment, Masking and Dispensing Randomisation Sequence A computer-generated randomisation list will be prepared by an independent statistician at LSHTM. This independent statistician will hold the sequence and will not be masked, however, they will not be involved in any other aspect of the study. The sequence will be in a 1:1 allocation ratio of CHX to NATA. To ensure reasonable balance in the allocation of treatments in different locations, the sequences will be blocked. The block size will vary randomly between 2, 4, and 6.

Following informed consent, patients attending either Kilimanjaro Christian Medical College or Mbarara Regional Referral Hospital with acute microbial keratitis will be included in stage 1 of the study. Stage 1 includes capturing demographic details, history of presenting complaint, examination and baseline investigations including microscopy, culture, in vivo confocal microscopy (IVCM), blood sugar levels and HIV serology. If these patients are found to have evidence of fungal keratitis (presence of hyphae on microscopy (light microscopy or IVCM) they will undergo Stage 2 consent and then be enrolled into the randomised clinical trial (providing they meet the inclusion/exclusion criteria). Data will be entered onto paper Clinical Record

Forms which will be scanned at the end of each day. Data will be double entered into an electronic database.

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Previous interventions:

Participants will be randomised to either topical chlorhexidine 0.2% or topical natamycin 5%. The treatment will be given hourly for one week, then two-hourly for a further two weeks. Ongoing treatment duration will then be tailored by clinical response. Follow-up assessments will be conducted at 2 days, 1 week, 2 weeks, 3 weeks, 2 months and 3 months, to determine the outcome. Randomisation, Allocation Concealment, Masking and Dispensing Randomisation Sequence A computer-generated randomisation list will be prepared by an independent statistician at LSHTM. This independent statistician will hold the sequence and will not be masked, however, they will not be involved in any other aspect of the study. The sequence will be in a 1:1 allocation ratio of CHX to NATA. To ensure reasonable balance in the allocation of treatments in different locations, the sequences will be blocked. The block size will vary randomly between 2, 4, and 6.

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Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Chlorhexidine 0.2% topical ophthalmic solution, Natamycin 5% topical ophthalmic suspension

Primary outcome measure
Best Spectacle Corrected Visual Acuity (BSCVA) measured at 3 months by a trial certified optometrist

Secondary outcome measures
1. Time to full epithelial healing (slit lamp examination by ophthalmologist at 2 days, 1 week, 2 weeks, 3 weeks, 2 months and 3 months)
2. Pin-hole visual acuity in logMAR at 3 months, trial-certified optometrist
3. Hard Contact Lens-corrected Visual Acuity measured in logMAR at 3 months
4. Scar/infiltrate size at 1 week, 3 weeks and 3 months (slit lamp examination by ophthalmologist)
5. Ulcer depth at 1 week and 3 weeks (slit lamp examination by ophthalmologist)

6. Hypopyon height at 1 and 3 weeks, (slit lamp examination by ophthalmologists)
7. Perforation and/or TPK by three months (slit lamp examination by ophthalmologist)
8. Positive culture rate assessed as the number of cases that test positive for fungus with microbiological culture, as a proportion of all cases of fungal keratitis at 1 week
9. Ocular adverse effects at each follow up visit (Day 2, Day 7, Day 14, 3 weeks, 2 months, 3 months), slit lamp examination by ophthalmologists
10. Quality of life (QoL) assessed using: EQ-5D, WHO/PBD-VF20, WHOQOL-BREF (comparison between baseline and QoL measures at 3 months)
11. Cost-effectiveness analysis, using EQ-5D data form 3 months and direct cost data
12. Drug adherence at each follow up visit (Day 2, Day 7, Day 14, 3 weeks, 2 months, 3 months) whilst the patient is using study medications

Overall study start date
01/04/2018

Completion date
31/12/2023

Eligibility

Key inclusion criteria
1. Acute microbial keratitis characterised by:
1.1 Corneal epithelial ulceration >1 mm diameter
1.2 Corneal stromal infiltrate
1.3 Acute inflammation: e.g. conjunctival injection, anterior chamber inflammatory cells, hypopyon
2. Filamentous fungal hyphae visualised on smear microscopy and/or in vivo confocal microscopy
3. Agree to be randomised to either treatment arm and able to give informed consent
4. Agree to be followed up at 2 days, 1 week, 2 weeks, 3 weeks, 2 months and 3 months
5. Adults (18 years and older)

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
358

Key exclusion criteria
Current exclusion criteria as of 08/09/2021:

1. Unwilling to participate in trial or attend follow-up
2. Aged less than 18 years
3. Pregnancy: self-reported, or by urine hCG pregnancy test if uncertain. 4. Breast feeding: selfreported
5. No light perception in the affected eye
6. Fellow eye visual acuity <6/60
7. Acanthamoebic infection visualised by smear microscopy or IVCM
8. Clinical evidence of herpetic keratitis
9. Known allergy to study medication (including preservatives)
10. Previous penetrating keratoplasty in the affected eye
11. Bilateral corneal ulcers
12. Nationals of another country
13. Very severe ulcers warranting immediate evisceration or conjunctival flap
14. Fungal Endophthalmitis

Previous exclusion criteria:

1. Pregnancy: self-reported, or by urine hCG pregnancy test if uncertain
2. Breast feeding: self-reported
3. Prior topical anti-fungal treatment
4. No light perception in the affected eye
5. Fellow eye visual acuity <6/60
6. Acanthamoebic infection visualised by smear microscopy or IVCM
7. Clinical evidence of herpetic keratitis
8. Known allergy to study medication (including preservatives)
9. Previous penetrating keratoplasty in the affected eye
10. Bilateral corneal ulcers
11. Very severe ulcers warranting immediate evisceration or conjunctival flap
12. Fungal Endophthalmitis

Date of first enrolment
01/06/2021

Date of final enrolment
30/05/2023

Locations

Countries of recruitment
Tanzania

Uganda

Study participating centre
Kilimanjaro Christian Medical Centre
Moshi
Moshi

Tanzania
PO Box 3010

Study participating centre
Mbarara Regional Referral Hospital
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Sponsor information

Organisation
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Sponsor type
University/education

Website
https://www.lshtm.ac.uk

ROR
https://ror.org/00a0jsq62

Funder(s)

Funder type
Charity

Funder Name
Wellcome Trust

Alternative Name(s)

Funding Body Type
Private sector organisation

Funding Body Subtype
International organizations

Location
United Kingdom

Results and Publications

Publication and dissemination plan
The data collected in this study will be reported to the College of Ophthalmologists of Eastern, Central and Southern Africa. Results will also be presented at international conferences. The results will be submitted for open access publication in peer-reviewed journals.

Intention to publish date
31/12/2024

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be available upon request from Prof Matthew Burton (matthew.burton@lshtm.ac.uk). The full data set will be available with all patient identifiable details removed. Data will be available after formal reporting of the study findings in a peer-reviewed scientific publication. Datasets will only be available to bona fide scientific investigators. Requests should be made to the Chief Investigator in writing detailing the scientific investigators background and intended use for the data. Consideration will be given to all proposed analyses, with likely envisaged uses including investigators planning on conducting meta-analyses for example. Patient Information Sheets and consent forms specifically referenced making anonymised data available and this has been approved by the relevant ethic committees.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet		22/03/2018	27/08/2020	No	Yes
Participant information sheet		26/01/2018	27/08/2020	No	Yes
Protocol article		28/03/2025	11/06/2025	Yes	No